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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/026,573	12/20/2001	Moshe Fleshner-Barak	1662/53003	9558

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EXAMINER
BENNETT, RACHEL M

ART UNIT	PAPER NUMBER
1615	11

DATE MAILED: 07/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/026,573	FLESHNER-BARAK ET AL.	
	Examin r	Art Unit	
	Rachel M. Bennett	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,7,10-12 and 31-50* is/are pending in the application.

4a) Of the above claim(s) *31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7,10-12,32-35 and 40-50* is/are rejected.

7)☒ Claim(s) *31, 36-39* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,6,8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The examiner acknowledges receipt of Amendment A filed 4/21/03.

Election/Restrictions

1. Applicant's election with traverse of Group I, Species I, solid oral dosage forms and Species II the antineoplastics agent irinotecan in Paper No. 10 is acknowledged. The traversal is on the ground(s) that all species are phase sensitive antineoplastics agents that could be used more efficaciously with frequent lower oral dosing as opposed to intermittent higher dosing by i.v. Moreover, each species suffer from reduced oral bioavailability due to deactivation of the PgP efflux pump. Lastly, four species does not constitute an unreasonable number under 37 CFR 1.146. This is not found persuasive because Species II contained 5 species. Applicants agree with the examiner that Applicant's claims to methods of cancer treatment by administering a gastric retention dosage form or composition in accordance with the invention containing irinotecan are clearly patentably distinct from the invention of Applicants' other claims. Therefore, claims 1-3, 7, 10-12 and 32-50 will be examined.

The requirement is still deemed proper and is therefore made FINAL.

Specification

Claim Objections

2. Claim 31 objected to because of the following informalities: Claim 31 depends on a cancelled claim. Appropriate correction is required.

3. Claims 36-39 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 1-3, 7, 10-11, 12, 32-35, 40-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over McGlynn et al. (US 2002/0136744 A1) and further in view of Kuhn, Pharmacology of Irinotecan.

Applicants claim a solid pharmaceutical dosage form for enhanced systemic delivery of irinotecan comprising irinotecan and a gastric retention vehicle composition comprising a hydrogel, wherein the dosage form expands upon contact with gastric fluid and wherein after ingestion by a patient the gastric retention vehicle composition expands to retain the dosage form in the patient's stomach for a prolonged period of time and methods of inhibiting cell proliferation in a tumor of a patient by orally administering a gastric retention solid dosage form.

McGlynn et al. disclose a drug delivery device for the sustained in situ production and release of a dispersion, in an environment of use which comprises a) a compressed core prepared

from an admixture comprising a therapeutically effective amount of a beneficial agent, a water swellable polymer, and a pH modulator and b) a water insoluble, water impermeable polymeric coating comprising a polymer and a plasticizers which surrounds and adheres to the compressed core, and water insoluble, water impermeable polymeric coating having at least one aperture. See abstract. The instant invention can achieve a sustained release of the beneficial agent, preferably over about a 6 to about an 8 hour period of time. The compressed core is an admixture of ingredients comprising a beneficial agent, a water swellable polymer which produces gelatinous microscopic particle when hydrated, a pH modulator and other ingredients that may affect any of (1) the rate of production of the dispersion; (2) the stability of the components of the dosage form; or (3) the mixing or compression characteristics of the admixture, is blended in such a way to produce a uniform material. This uniform material is then compressed, within a die, to produce a desired form, normally in the shape of a tablet, capsule, or bolus. See page 2. The beneficial agent is in an amount from about 5 mg to about 500 mg. Upon hydration, the hydrated gel is forced out of he compressed core due to the volume expansion of the polymer within the compressed core. This water swellable polymer is capable of swelling in the gastric intestinal fluid. See page 5. Other compounds that can be used as polymer hydration modifiers include glucose (sugar moiety of tannic acid). See Page 5. Other excipients include polyvinylpyrrolidone. See page 6. Preferably, the film coating comprises hydroxylpropyl methyl cellulose. The drug delivery device may also be co-administered with other well know therapeutic agents that are selected for their particular usefulness against the condition being treated. Antineoplastic agents are known to be used in methods of treating cancer and/or tumors. Specific agents disclosed are camptothecin and CPT-11 (irinotecan). See

page 8. McGlynn does not disclose at least a portion of the released irinotecan is converted into a metabolite before it is absorbed into the patient's bloodstream.

Kuhn discloses irinotecan (CPT-11) is a semisynthetic, water-soluble camptothecin derivative recently approved in the US for the second-line treatment of patients with metastatic colorectal carcinoma. Irinotecan is a prodrug that is bioactivated by carboxylesterases to the topoisomerase I inhibitor, a minor metabolite, SN-38. Both irinotecan and SN-38 are in equilibrium with their active lactone and inactive hydroxy acid forms. This equilibrium is both pH and protein dependent. Oxidation by CYP3A4 of the terminal piperidine ring of irinotecan yields the major metabolite, aminopentanecarboxylic acid (APC). SN-38 is clucoronidated by uridine glucuronidase. See Page 39. The oral route of administration may be an option that is pharmacologically suited to the highly schedule-dependent activity of irinotecan. The high concentration of tissue carboxylesterases in the gastrointestinal tract and liver could promote the presystemic conversion of irinotecan to SN-38. In addition, the low gastric and upper intestinal pH should favor the retention of irinotecan and SN-38 in the active lactone ring configuration. The molar ratio of SN-38 area under the curve (AUC) to irinotecan AUC was threefold higher after oral administration of irinotecan that after intravenous administration.

Absent unexpected results, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have expected the composition taught by McGlynn comprising irinotecan to have at least a portion of the released irinotecan converted into a metabolite before it is absorbed into the patient's bloodstream, wherein the metabolite can exist in an active lactone form and an inactive hydroxyl acid form because Kuhn teaches both irinotecan and SN-38 are in equilibrium with their active lactone and inactive hydroxy acid

forms. This equilibrium is both pH and protein dependent. Therefore, one of ordinary skill in the art would expect the irinotecan released in the patient's gastric intestinal fluid, as taught by McGlynn, to exist in both the active lactone form and an inactive hydroxyl acid form before it enters the patient bloodstream.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rachel M. Bennett whose telephone number is (703) 308-8779. The examiner can normally be reached on Monday through Friday, 8:00 A.M. to 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on (703) 308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3592 for regular communications and (703) 308-7924 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

rmb
July 2, 2003

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600